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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,446	06/20/2005	Zhiwen Zhou	Q88152	8654

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,446	ZHOU ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 12-19-08.

Claims 1-7 and 9-12 are pending in the instant application.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy was filed in the parent PCT/ICN03/01068 and was again filed on 6-20-05 in the instant application. Support for the instantly claimed sequence, SEQ ID No. 3 is shown on page 2 of the priority document. The priority date for the instantly claimed invention is December 18, 2002.

Election/Restrictions

This application contains claims SEQ ID Nos. 1 and 2, drawn to an invention nonelected with traverse in the reply filed on 6-23-08. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant argues that an improper legal standard has been used to restrict the instant claims to a single SEQ ID NO. because the claims comprising all of the sequences claimed do not lack unity and an allegation of an undue search burden are insufficient grounds to support a lack of unity of invention, and thus restriction. Contrary to Applicant's assertions, the instant sequences are chemically, functionally, and structurally distinct and different and thus are distinct inventions. One does not render

the other obvious. Furthermore, a search of one sequence would not be coextensive with the searches required for each of the other sequences. For these reasons, as well as the undue search burden imposed by searching the patent and non-patent data bases for each of the sequences claimed, the restriction is hereby maintained.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby maintained.

Applicant's arguments with respect to claims 1-7 and 9-12 have been considered but are moot in view of the new ground(s) of rejection set forth below.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods for the prevention or treatment of HIV infection or prevention or treatment of AIDS comprising administration

of a composition comprising a liposomal formulation and either a single stranded RNA or a double stranded RNA comprising SEQ ID NO. 3, or optionally comprising a fragment between 19 and 28 nucleotides of SEQ ID NO. 3, which RNA optionally further comprises two uracil nucleotides on the 5' or 3' termini, and which double stranded RNA optionally further comprises a hairpin RNA consisting of a stem part and a loop part.

The specification and claims do not adequately describe the concise structural features comprising this genus of inhibitory molecules that provide for the function claimed, or preventing or treating HIV infection or AIDS in a subject. The specification teaches the in vitro inhibition of expression of HIV envelope by the siRNA molecules shown in the Table on page 8 of the instant specification. These molecules, however, do not include SEQ ID NO. 3 or the fragments of SEQ ID NO. 3 as instantly claimed.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus of inhibitory molecules claimed, encompassing a single stranded RNA or a double stranded RNA comprising SEQ ID NO. 3, or optionally comprising a fragment between 19 and 28 nucleotides of SEQ ID NO. 3, which RNA optionally further comprises two uracil nucleotides on the 5' or 3' termini, and which double stranded RNA optionally further comprises a hairpin RNA consisting of a stem part and a loop part, and which provide for the function claimed, of providing prevention or treatment of HIV infection or AIDS in a patient. Thus, Applicant was not in possession of the claimed genus. One of skill in the art would reasonably conclude that adequate written description is lacking for the instantly claimed genus of inhibitory compounds claimed.

Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of expression of HIV envelope by the siRNA molecules shown in the Table on page 8 of the instant specification, does not reasonably provide enablement for methods of preventing or treating HIV infection or AIDS comprising administration of a composition comprising a liposomal formulation and either a single stranded RNA or a double stranded RNA comprising SEQ ID NO. 3, or optionally comprising a fragment between 19 and 28 nucleotides of SEQ ID NO. 3, which RNA optionally further comprises two uracil nucleotides on the 5' or 3' termini, and which double stranded RNA optionally further comprises a hairpin RNA consisting of a stem part and a loop part. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods for the prevention or treatment of HIV infection or prevention or treatment of AIDS comprising administration of a composition comprising a liposomal formulation and either a single stranded RNA or a double stranded RNA comprising SEQ ID NO. 3, or optionally comprising a fragment between 19 and 28 nucleotides of SEQ ID NO. 3, which RNA optionally further comprises two uracil nucleotides on the 5' or 3' termini, and which double stranded RNA optionally further comprises a hairpin RNA consisting of a stem part and a loop part.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of nucleic acid treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50; *see* entire text for Branch; S. Crooke, Annu. Rev. Med., Vol. 55, pages 61-95, 2004, esp. at pages 71, 72, 74, 81 and 84).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of treating or preventing HIV or AIDS in a subject comprising the administration of a representative number of members of the genus of inhibitory compounds claimed. Applicants have not provided guidance toward a method of preventing or treating HIV or AIDS in a subject comprising the administration of siRNA comprising SEQ ID NO. 3 and its complement, or comprising fragments of SEQ ID NO. 3.

The specification teaches the in vitro inhibition of expression of HIV envelope by the siRNA molecules shown in the Table on page 8 of the instant specification. These molecules, however, do not include SEQ ID NO. 3 or the fragments of SEQ ID NO. 3

instantly claimed. These teachings in the instant disclosure, however, are not representative or correlative of the ability to achieve in vivo inhibition of expression of HIV, or treatment or prophylactic effects comprising the administration of a liposomal formulation and either a single stranded RNA or a double stranded RNA comprising SEQ ID NO. 3, or optionally comprising a fragment between 19 and 28 nucleotides of SEQ ID NO. 3, which RNA optionally further comprises two uracil nucleotides on the 5' or 3' termini, and which double stranded RNA optionally further comprises a hairpin RNA consisting of a stem part and a loop part. One skilled in the art would not accept on its face the examples given in the specification of in vitro inhibition using the siRNA molecules disclosed in the Table on page 8 of the instant specification, as being correlative or representative of the successful prevention or treatment of HIV or AIDS in a subject comprising administration of SEQ ID NO. 3, or any of its fragments as instantly claimed. This is in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of therapeutic nucleic acid molecules, administered via any route to a subject. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by the claimed genus of inhibitory molecules, and specifically regarding the instant compositions comprising fragments of SEQ ID No. 3, either single stranded or double stranded.

The breadth of the claims and the quantity of experimentation required.

The claims are drawn to methods for the prevention or treatment of HIV infection or prevention or treatment of AIDS comprising administration of a composition comprising

a liposomal formulation and either a single stranded RNA or a double stranded RNA comprising SEQ ID NO. 3, or optionally comprising a fragment between 19 and 28 nucleotides of SEQ ID NO. 3, which RNA optionally further comprises two uracil nucleotides on the 5' or 3' termini, and which double stranded RNA optionally further comprises a hairpin RNA consisting of a stem part and a loop part.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target HIV, whereby its expression is inhibited in vivo comprising administration of a representative number of species of the genus of inhibitory compounds claimed, and further whereby treatment and prophylactic effects are provided in a subject. Since the specification fails to provide any particular guidance for the successful targeting and inhibition of expression of HIV in vivo comprising administration of any nucleic acids encompassed by the genus claimed, or for the successful treatment or prevention of HIV or AIDS in an organism following administration of any nucleic acid encompassed by the genus claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94

(December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Douglas) Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
3-13-09

/Jane Zara/

Primary Examiner, Art Unit 1635